Idiopatic acquired hemophilia A in two women in Chioggia

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ABSTRACT

Acquired hemophilia A (AHA) is a rare, but often life-threatening hemorrhagic disorder characterized by antibodies directed against coagulation factor VIII. We report clinical and laboratory investigations of two cases with AHA observed in our hospital. These patients were two elderly women (73 and 62 years old), who presented with subcutaneous bleeding, intramuscular hematoma and a prolonged activated partial thromboplastin time (aPTT). On the basis of these findings as well as decreased factor VIII activities and the presence of factor VIII inhibitors, we made a diagnosis of AHA. Both patients were referred to a specialized hospital for treatment. The diagnosis of AHA should be considered in any elderly patient who presents with bleeding and prolonged aPTT. Moreover, the coexistence of a series of underlying diseases associated with AHA should be always searched for.

INTRODUCTION

Acquired hemophilia A (AHA) is a rare disease, with an estimated annual incidence of 1-2 cases per million per year. This potentially life-threatening bleeding disorder is caused by the development of autoantibodies, usually IgGk4, directed against circulating factor VIII (FVIII) of coagulation (1-4). Age distribution is bimodal, with a first peak occurring among young adults, due to cases in women in the postpartum period, and a second major peak in elderly persons. In ~50% of cases, FVIII autoantibodies may be associated with autoimmune disease, hematologic malignancies, solid cancers, infections or use of medications, while the remaining 50% of cases occur in patients lacking any relevant concomitant disease, so being defined “idiopathic” (5, 6).

The pattern of bleeding in AHA differs from that in congenital hemophilia A that is mainly characterized by hemarthoses. In AHA bleeding tends to occur in soft tissue, muscle, retroperitoneal space and gastrointestinal or genitourinary tracts; hemarthroses are rare. Rates of mortality from acquired hemophilia up to 44% have been reported, with most deaths occurring in the first few weeks. Thus, a prompt recognition of this disorder and an early and aggressive treatment are mandatory, as diagnostic delay or inadequate treatments are associated with high mortality rates (7). In this paper, we report clinical features, laboratory findings and treatment of two women with a history of bleeding occurring in the elderly in whom AHA was diagnosed.

METHODS

Coagulation study was performed by using a Sysmex CA7000 analyzer and commercial reagents (Dasit) for prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen, D-dimer, antithrombin (AT), protein C, protein S, heparin quantification and lupus anticoagulant (LAK) (8). Activity of FVIII was measured on CA7000 using a modification of the one-stage aPTT test. Other coagulation factors were measured according to Valverde et al. (8). Von Willebrand factor antigen (VWF:Ag) was measured by a commercial automated enzyme-linked immunosorbent assay on a Vidas analyzer (bioMerieux).

For mixing studies, the patient’s plasma was mixed with an equal volume of normal pool (10 normal donors plasma pooled and stored at -80 °C), an aPTT was performed immediately after pooling (t0) and after incubation for 120 min at 37 °C (t120), noting the degree of correction. Correction of the abnormality indicates that the added plasma contains the deficient factor from the test sample, whereas a persisting abnormality might

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signify the presence of inhibitors or LAK (9, 10).

Presence of LAK was also evaluated with two functional tests and with a commercial automated test (Instrumentation Laboratory) by testing patients' sera for anti-cardiolipin IgG and IgM, anti-prothrombin IgG and IgM, anti-β_2-glicoprotein 1 IgG and IgM (11). Inhibitor assays were performed using the Bethesda method, according to the Nijmegen modification (12, 13). In brief, serial dilutions by FVIII assay buffer of the patient's plasma were prepared. A standardized amount of FVIII in the form of a normal plasma pool was added to each dilution of test plasma. In the FVIII assay, carried out after 2 h of incubation, the control mix of normal plasma and buffer was used as the standard reference and FVIII concentrations of other mixtures calculated against this. At the end of the incubation period, the residual FVIII level was measured by coagulant FVIII activity assay and the inhibitor calculated from a graph of residual FVIII vs. inhibitor units.

Diagnosis of AHA was confirmed in presence of a long aPTT without any correction after mixing, a very low FVIII concentration (<5%) and demonstration of a specific inhibitor presence. A written informed consent was obtained from the two patients before the preparation of this case report.

CASE 1

A 73-years old woman came to our attention for massive ecchymoses presented with multiple spontaneous hematomas (gluteal, neck and lower limbs) in the absence of personal or family history of bleeding or clotting disorders. Her medical history included type 2 diabetes mellitus, arterial hypertension and mild renal failure. She was taking glibenclamide and losartan. Spontaneous ecchymoses in both arms were noted three weeks before the admission. These cutaneous hemorrhages were more and more extended and gradually involved lower limbs. The day before admission most of the skin of limbs was covered, also spreading to the abdomen and thorax. Submucosal petechiae also appeared in mouth and a conjunctiva hemorrhage in the right eye.

On admission, laboratory investigations revealed mild anemia (hemoglobin, 123 g/L) and normal platelet count (219 × 10^9/L); plasma creatinine was 2.20 mg/dL and glucose 125 mg/dL. Coagulation tests showed a prolonged aPTT (92 s, ratio 2.73) with normal PT, fibrinogen and TT; D-dimer was moderately increased. aPTT was not modified after mixing test; LAK was negative, FVIII activity was <1% and the presence of a FVIII inhibitor was confirmed with a concentration of 12 BU/mL, leading to diagnosing AHA. Other coagulation tests were unaltered.

After diagnosis of AHA the patient was transferred to a reference center for hemophilic patients, where she was treated with activated recombinant factor VII (rFVIIa) concentrate to control hemorrhages. Concomitantly, immunosuppressive therapy with prednisone and cyclophosphamide was started. After failure of this first line approach and relapse in FVIII inhibitor concentration, anti-CD20 (rituximab) was added. Clinical and laboratory features improved in the following weeks, with a progressive normalization of the aPTT and the eradication of the FVIII inhibitor (Figure 1).

CASE 2

A woman of 62 years was presented to our emergency department for a major spontaneous intramuscular hematoma of the right arm in the absence of personal or family history of bleeding or clotting disorders. Her past medical history included type 2 diabetes and arterial hypertension treated with glimepiride and metformin. The month before, she was cured for back pain treated with anti-inflammatory drugs. After an ultrasound diagnosis of fasciitis, a blood culture was performed and broad-spectrum antibiotic therapy started.

On admission, laboratory investigations revealed neutrophilic leukocytosis (15.000/μL) mild anemia (hemoglobin, 102 g/L) and normal platelet count (389 × 10^9/L). Coagulation tests showed a prolonged aPTT (53 s, ratio 1.55) with normal PT, fibrinogen and TT; D-dimer was moderately increased. On the third day after admission a large hematoma of the left lower limb was developed. An ultrasound scan of the leg was made to exclude thrombovenous embolism. The anemia worsened (hemoglobin, 60 g/L) and the patient had to be transfused with 4 units of red cell concentrate. On the fifth day the patient suddenly accused worsening dyspnea and dysphonia. An otolaryngology consultation showed the presence of a large submucosal hematoma of pharynx and larynx, confirmed by computerized tomography scan (Figure 2). Coagulation tests showed a prolonged aPTT (79 s, ratio 2.32), with normal PT, fibrinogen and TT. D-dimer was elevated. aPTT was not

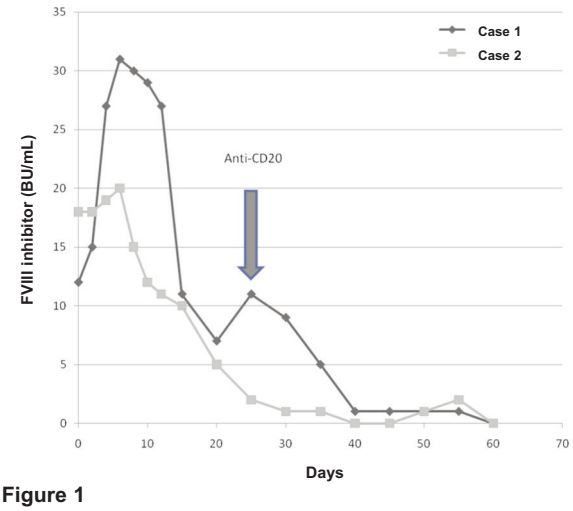

Figure 1

Course of factor VIII (FVIII) inhibitor concentrations in the two studied cases of acquired hemophilia A. Both cases were treated with prednisone and cyclophosphamide as first line therapy. In case 1 a relapse in FVIII inhibitor concentrations was observed after 24 days and anti-CD20 therapy was added.

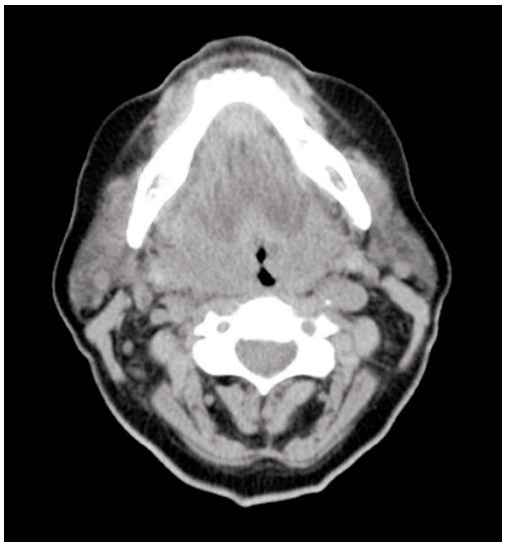

Figure 2
Direct computerized tomography scan at mandibular level of case 2 showing thickening and obliteration of the adipose parapharingeal spaces. They have the same level of density in comparison with the contiguous muscular structures of the neck with which they are not well differentiable. The evidence of a reduction of the transversal diameter of the pharyngeal lumen suggests a compression effect due to the thickening of the contiguous soft tissues; no evidence of masses.

modified after mixing test, LAK was negative, FVIII activity was 5% and the presence of a FVIII inhibitor was confirmed with a concentration of 18 BU/mL, leading to diagnosing AHA. Other coagulation tests were normal. Due to the worsening of the clinical situation and problems in ventilation it was necessary to perform an emergency tracheotomy and to transfer the patient to a specialized center for the intensive treatment of bleeding disorders. After stabilization of the clinical condition, control of bleeding by using rFVIIa and immunosuppressive therapy with prednisone and cyclophosphamide was started. Clinical and laboratory features improved in the following weeks, with a progressive normalization of aPTT and the eradication of the FVIII inhibitor (Figure 1).

DISCUSSION

AHA is a rare, but life-threatening bleeding disorder, typically occurring in the elderly (>80% of diagnosed patients are aged >60 years). The diagnosis of AHA should be considered in elderly patients who presents with a recent history of bleeding and an isolated prolonged aPTT (14). Usually, in AHA post-traumatic and iatrogenic hemorrhage are observed; cutaneous and mucosal spontaneous hemorrhage and intramuscular hematomas are also frequently reported (15). These patients usually had normal PT, TT and fibrinogen concentrations, but an increase in D-dimer concentrations is often reported and is related to hematoma presence. Indeed, a prolonged aPTT may be attributable to coagulation factor deficiencies or to a coagulation inhibitor such as LAK, heparin therapy or, rarely, to an autoimmune coagulation factor inhibitor (16). The mixing test is a simple assay able to discriminate if a prolonged aPTT is due to coagulation factor deficiency (correction of aPTT after mixing) or to presence of inhibitors of coagulation (absence of aPTT correction after mixing). The presence of LAK may also be associated with a prolonged aPTT that is not corrected with normal plasma, but in this case no bleeding tendency is shown (9, 10).

In our cases, we performed quantitative coagulation factor assays that revealed a reduced level of FVIII with normal values of factor IX. These results confirmed the presence of an inhibitor against FVIII and, therefore, suggested the diagnosis of AHA. This diagnosis was then further confirmed by the demonstration and quantification in both patients of an autoantibody directed against FVIII. It is noteworthy that for demonstration of a FVIII inhibitor by using the Bethesda method and quantification of FVIII there is a need of a second level laboratory approach; on the other hand, the mixing test may be easily carried out in all laboratories, allowing the identification of patients who require further investigations (17).

When AHA is diagnosed, the possible coexistence of an underlying disease responsible for this immunologic complication should be suspected and intensively searched for. In particular, in elderly patients AHA is often secondary to hematologic or solid malignancy or drug administration (e.g., antibiotics, phenytoin, methyldopa, interferon, fludarabine and clopidogrel). However, about half of the cases are apparently idiopathic, although in some patients an underlying disorder may be diagnosed long after the onset of the bleeding abnormality. In both our patients it was impossible to detect any underlying disease, so both were classified as primary or idiopathic AHA (18, 19).

Our case reports confirm the complexity of diagnosis and management of AHA in elderly patients, in whom the clinical picture is complicated by comorbidities and concomitant drug intake. The latter may facilitate bleeding complications or delay the diagnosis, when antiplatelet or anticoagulant drugs are administered. The coexistence in AHA patients, in particular in the elderly, of overt cardiovascular or thromboembolic diseases requiring antithrombotic treatment, represents a challenging issue in this setting. The occurrence of severe bleeding leads to the withdrawal of such treatments and in many cases to the administration of bypassing agents (e.g. rFVIIa), with possible increase of thromboembolic risk. This risk is further enhanced by the reduced mobility due to hospitalization or muscle bleeding. Thus, an accurate balance between bleeding and thrombotic risk should be carefully taken into account when these patients are treated for the bleeding complications, by modulating doses and duration of bypassing agent administration. According to recent recommendations, bypassing agents should not be considered contraindicated in the presence of severe or

life-threatening bleeding and in patients at thromboembolic risk too (12, 15).

In AHA early diagnosis and an appropriate therapeutic approach is crucial for a favorable outcome. Bleeding complications are fatal in 10%-20% of cases; therefore, patients with AHA should be managed by a hemophilia center with laboratory and clinical experience in this setting, because of the complexity of treatment. Immunosuppressive regimens in the elderly should aim to eradicate the inhibitor as rapidly as possible, reducing the time of exposure to the side effects of immunosuppressive therapy. Prednisone remains the first-line treatment, usually in combination with cyclophosphamide. Other approaches, for example rituximab, may be considered when first-line immunosuppressive treatment fails or is contraindicated (20).

CONFLICTS OF INTEREST

No authors declared any potential conflicts of interest.

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